IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	**HAMADA, Katsuyuki *et al.***
App. No.	:	**10/576,047**
Filed	:	**April 14, 2006**
For	:	**Cancer Gene Therapeutic Drug**
Examiner	:	**Hill, Kevin Kai**
Group Art Unit	:	**1633**

RESPONSE TO FINAL REJECTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Response is to the Final Rejection mailed August 22, 2008 with a request for a 1-month extension and submitted with payment of the fee for a One Month extension. Applicant respectfully requests the Examiner to enter the Amendments to the Claims and consider the arguments as to the allowability of the claims.

Amendments to the Claims are reflected in the listing of claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the Application. Deletions are ~~strikethrough~~ and additions are underlined.

Listing of Claims:

1. (Canceled)

2. (Previously presented) The drug kit for cancer therapy of claim 24, wherein the virus for immunological treatment and the oncolytic virus are selected from the group consisting of adenovirus, herpes virus, lentivirus, HIV virus, retrovirus, reovirus, vesicular stomatitis virus (VSV) and any other oncolytic virus.

3. (Canceled)

4. (Previously presented) The drug kit for cancer therapy of claim 24, wherein the carrier cell is selected from the group consisting of an A549 cell, 293 cell, SW626 cell, HT-3 cell, PA-1 cell, human derived cancer cell, and human normal cell.

5. (Previously presented) The drug kit for cancer therapy of claim 24, wherein the oncolytic virus has a promoter selected from the group consisting of 1A1.3B promoter, midkine promoter, β-HCG promoter, SCCA1 promoter, cox-2 promoter, PSA promoter and a tumor specific promoter according to the type of cancer to be treated.

6. (Previously presented) The drug kit for cancer therapy of claim 24, further comprising:

(i) atelocollagen.

7. (Withdrawn) The drug kit for cancer therapy of claim 24, further comprising:

(i) a GM-CSF expression vector, which when grown with the carrier cell, the carrier cell becomes infected with the GM-CSF expression virus vector.

8. (Withdrawn) The drug kit for cancer therapy of claim 24, further comprising: at least one composition selected from the group consisting of,

(i) an iron preparation and

(ii) a porphyrin compound.

9. (Withdrawn) The drug kit for cancer therapy of claim 24, further comprising:

(i) a tumor cell, which is administered to the animal for tumor vaccination.

10. (Canceled)

11. (Previously presented) The method of cancer gene therapy of claim 25, wherein the period after administering the virus for immunological treatment is within the range of about two weeks to not more than 13 weeks.

12. (Currently amended) The method of cancer gene therapy of claim 25, wherein the virus for immunological treatment is administered in an amount between about 10^5 viral particles and 10^{11} viral particles to a patient who is negative for the antibodies to the virus, and is administered in an amount between about 10^2 viral particles and 10^7 viral particles ~~to 0 viral particles~~ to a patient who is positive for the antibodies to the virus.

13. (Withdrawn) The method of cancer gene therapy of claim 25, wherein the oncolytic virus infected carrier cell delivers an amount of oncolytic virus between about 10^9 viral particles and 10^{14} viral particles to the patient.

14. (Withdrawn) The method of cancer gene therapy of claim 25, wherein the oncolytic virus infected carrier cell has an amount of viral particles between about 0.1 viral particles/cell and 2,000 viral particles/cell.

15. (Previously presented) The method of cancer gene therapy of claim 25, where the administering of the oncolytic virus infected carrier cell is by intratumor injection.

16. (Previously presented) The method of cancer gene therapy of claim 25, further comprising: administering atelocollagen with the oncolytic virus infected carrier cell in step (d).

17. (Withdrawn) The method of cancer gene therapy of claim 25, where the carrier cell in step (c) is grown with an oncolytic virus and GM-CSF expression virus vector to produce a carrier cell infected with an oncolytic virus and a GM-CSF expression virus vector.

18. (Withdrawn) The method of cancer gene therapy of claim 25, further comprising administering at least one composition selected from the group consisting of an iron preparation and a porphyrin compound, with the oncolytic virus infected carrier cell in step (d).

19. (Withdrawn) The method of cancer gene therapy of claim 25, further comprising administering a tumor cell to produce tumor vaccination, at a time selected from the group consisting of; before, after and concurrent administering the virus for immunological treatment.

20. (Canceled)

21. (Previously presented) The drug kit for cancer therapy of cancer gene therapeutic drug according to claim 2, wherein the carrier cell is selected from the group consisting of an A549 cell, 293 cell, SW626 cell, HT-3 cell, PA-1 cell, human derived cancer cell, and human normal cell.

22 – 23. (Canceled)

24. (Currently amended) A drug kit for cancer therapy comprising:

(a) a <u>non-proliferative</u> virus for immunological treatment, which when administered to an animal produces a Cytotoxic T lymphocytes (CTL) reaction within the animal after administering a carrier cell ~~and which is non-proliferative~~;

(b) the carrier cell, which when grown with an oncolytic virus becomes infected with the oncolytic virus so when the carrier cell is administered to the animal the oncolytic virus acts on a tumor cell within the animal; and

(c) the oncolytic virus, which is the same type of virus as the virus for immunological treatment and which is proliferative in the tumor cell.

25. (Currently amended) A method of cancer gene therapy comprising:

(a) administering a non-proliferative virus for immunological treatment to a patient to induce a Cytotoxic T lymphocytes (CTL) reaction within the patient after administering a carrier cell~~, wherein the virus for immunological treatment is non-proliferative~~;

(b) waiting a period after administering the virus for immunological treatment before continuing with the method of cancer gene therapy;

(c) after waiting the period, growing a carrier cell with an oncolytic virus to produce an oncolytic virus infected carrier cell, wherein the oncolytic virus is the same type of virus as the virus for immunological treatment; and

(d) administering the oncolytic virus infected carrier cell, at least one time, to the patient to make the oncolytic virus act on a tumor cell within the patient, and wherein the oncolytic virus is proliferative in the tumor cell.

REMARKS/ARGUMENTS

Claim Objections - Claims 3 - 4, 10 and 21 – 25

Claims 24 - 25

The Office Action suggested placing the adjective "non-proliferative" closer to its noun "virus".

Applicants have amended Claims 24 and 25 to more clearly claim the virus as a "non-proliferative virus" as suggested by the Examiner.

Claims 3 and 20

Applicants have canceled Claims 3 and 20.

Claims 21 and 23

Applicants have canceled Claim 23.

Claims 4 and 22

Applicants have canceled Claim 22.

Claims

35 U.S.C. § 112 ¶ 2 Rejections - Claim 12

The Office Action rejected Claim 12 under 35 U.S.C. § 112 ¶ 1 because the specification as originally filed does not describe the invention as now claimed. The Office Action stated "Claim 12 recites that the virus is administered in an amount "to 0 viral particles to a patient who is positive for the antibodies to the virus".

Applicants have amended Claim 12 to more clearly claim the amount of viral particles as "between about 10^2 viral particles and 10^7 viral particles". Support for this amendment can be found at least at Page 4, Paragraph 5, line 6 -7 of the Substitute Specification filed on February 18, 2008.

35 U.S.C. § 102(e) Rejection of Claims 2 - 3, 11 – 12, 15, 20 and 24 – 25

The Office Action rejected Claims 2 – 3, 11 – 12, 15, 20 and 24 - 25 under 35 U.S.C. 102(e) as being anticipated by Terman, 2002/0177551 Al. The Office Action stated "With respect to claims 24 and 25, Terman '551 discloses a cancer therapeutic drug and a method of

treating tumors…, the method comprising a step of administering to a patient *in vivo* with a nucleic acid viral vector to induce a CTL reaction to a carrier cell expressing one or more desired antigens .., and after a predetermined period of time, the method further comprising a step of administering to said patient carrier cells infected with an oncolytic virus .."

The Applicants disagree with the conclusion of the Office Action that Terman '551 discloses, each and every feature, of Claims 24 and 25; and Traverse.

Claim 24

Claim 24 is a claim to a "kit" containing the following items:

(a) a non-proliferative virus for immunological treatment

(b) a carrier cell

(c) the oncolytic virus

Terman '551 does not disclose a kit or container that includes all three items needed to practice the method in Claim 25. It is not sufficient to pick and choose through a reference to combine the necessary items to produce a hypothetical "kit" that was never envisioned by the author. Additionally, Terman '551 does not disclose a virus which is available for use in both forms: non-proliferative and oncolytic.

The disclosure of Terman '551 would not enable a person skilled in the art to first, obtain the three necessary items, and then second, to combine those specific items into a kit for practicing the method of Claim 25.

Claim 25

Claim 25 is a claim to a method of cancer gene therapy with 4 steps:

(a) administering a non-proliferative virus

(b) waiting a period

(c) growing a carrier cell with an oncolytic virus

(d) administering the oncolytic virus infected carrier cell

Terman '551 does not disclose a method with these 4 steps and with the steps in this order. It is not sufficient to pick and choose various actions in a specification, and place them in

an order disclosed in the present application. The cited reference must disclose the specific steps in the specific order, before it can be used as a reference disclosing the claimed method in the present application.

In *Net MoneyIn v. Verisign* (CAFC 2007-1565, decided October 20, 2008) the court ruled that anticipation takes more than simply locating each element within the four corners of a single document. To anticipate, the prior art must teach all the claim elements and the claimed arrangement. Focusing for a moment on arrangement – to anticipate, the reference must teach "all of the limitations arranged or combined in the same way as recited in the claim."

> *Section 102 embodies the concept of novelty—if a device or process has been previously invented (and disclosed to the public), then it is not new, and therefore the claimed invention is "anticipated" by the prior invention. . . . Because the hallmark of anticipation is prior invention, the prior art reference—in order to anticipate under 35 U.S.C. § 102—must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements "arranged as in the claim."* [page 14, para. 2 to page 15, line 7]

The opinion states at page 15, first full paragraph, "The meaning of the expression 'arranged as in the claim' is readily understood in relation to claims drawn to things such as ingredients mixed in some claimed order. In such instances, a reference that discloses all of the claimed ingredients, but not in the order claimed, would not anticipate, because the reference would be missing any disclosure of the limitations of the claimed invention 'arranged as in the claim.'"

Therefore, Terman '551 does not disclose the claimed method or enable a person skilled in the art to develop the disclosed method.

The present application discloses and claims the use of the immunological reaction of the "virus" that is generated by administering a non-proliferative form of the virus. Terman '551 is generating a reaction to the SAg that is conjugated to a virus. There is no immunological reaction to the virus.

The Office Action alleges that Terman '551 discloses on page 9 [0069 -70] that the virus for immunological treatment may be administered *in vivo*, without first being used to transfect a

cell *in vitro* (e.g. pg 9, [0069-70]; pg 11, [0086]). A careful reading of these paragraphs indicate two points: 1) the *in vivo* administering disclosed in paragraphs [0069-70] is to transfect the cells of the host, rather than to cause an immunological reaction, and 2) the immunization disclosed in paragraph [0086] is to SAg rather than a non-proliferative virus.

The invention disclosed in Terman '551 is directed to a conjugate comprising superantigen polypeptides [SAg] (such as staphylococcal enterotoxins), and nucleic acids with other structures that preferentially bind to tumor cells and are capable of inducing apoptosis. Terman '551 discloses in [0051] that cells transfected with nucleic acid that encodes a SAg polypeptide are used as a vaccine to immunize a host against a cancer previously present in the host or a cancer that is likely to develop in the host. It is clear that the immunization intended in Terman '551 is an immunization against SAg.

Comparatively, the immunological treatment of the present invention is conducted by a non-proliferative virus (component (a) above), which is the same type of oncolytic virus (component (c) above) to be administered with carrier cells afterwards. Terman '551 does not disclose the features of the present invention, namely, using the same virus in the immunization of the patient and in infecting carrier cells to be administered, to induce a CTL response in a living body after administering the infected carrier cells.

Therefore, Terman '551 does not disclose or teach the cancer gene therapy method conducted according to steps (a) to (d) recited in Claim 25 of the present application.

35 U.S.C. § 103(a) Rejection of Claims 2 – 4, 11 – 12, 15 and 20 - 25

The Office Action rejected Claims 2 – 4, 11 – 12, 15 and 20 - 25 under 35 U.S.C. 103(a) as being obvious over Terman (2002/0177551 Al) and Harrison *et al.* (Human Gene Therapy 12(10):1323-1332, 2001). The Office Action stated "Terman does not disclose the carrier cell to be an A549 cell. However, at the time of the invention, Harrison *et al.* taught the use of A549 cells to produce oncolytic adenoviruses in a method to treat tumors."

The Applicants disagree with the conclusion of the Office Action that the combination of Terman '551 and Harrison *et al.* discloses, each and every feature, of Claims 2 – 4, 11 – 12, 15 and 20 – 25, and Traverse.

Claims 2 – 4 and 21 depend on Claim 24, and Claims 11, 12 and 15 depend on Claim 25. Claims 24 and 25 are patentable over Terman '551; therefore, these claims are also patentable over Terman '551.

As discussed above, Terman '551 does not disclose, each and every feature, of Independent Claims 24 and 25, and Harrison *et al.* does not disclose those features which are deficient in Terman '551. Therefore, the disclosure of Harrison *et al.* is not sufficient to make obvious the claims dependent from Claims 24 and 25.

The Office Action stated that Harrison *et al.* discloses the use of A549 cells for the production of adenovirus in the treatment of tumors. However, Harrison *et al.* only teaches that A549 cells can be used in the production of mouse tumor models. Harrison *et al.* does not disclose that A549 cells can be used as carrier cells in the treatment of tumors.

Biological functions and cellular reactions are an unpredictable art and, as such, it is impossible to predict what will result if parameters are changed. There is a large difference in the biochemical and cellular functions between the disclosure of Harrison *et al.* of using A549 cells to produce adenovirus and the use of A549 cells as carrier cells to treat tumors, as disclosed in the present application.

Neither, Terman '551 nor Harrison *et al.* discloses the use of an A549 cell line as a carrier cell; therefore, a person skilled art would not be enabled to practice the present invention based on the disclosures of these references. Claims 24 and 25 are patentable over Terman '551, in combination with Harrison *et al.*

Claims 2, 4, and 21 depend on Claim 24, and Claims 11, 12 and 15 depend on Claim 25. Therefore, these claims are also patentable over Terman '551 and Harrison *et al.*

The Examiner is requested to withdraw the combination of Terman '551 and Harrison *et al.* as 103(a) Prior Art references. In light of the foregoing arguments and amendments to the claims, the Examiner is respectfully requested to allow Claims 2 – 4, 11 – 12, 15 and 20 – 25.

35 U.S.C. § 103(a) Rejection of Claims 6 and 16

The Office Action rejected Claims 6 and 16 under 35 U.S.C. 103(a) as being obvious over Terman (2002/017755 1 Al) and Harrison *et al.* (Human Gene Therapy 12(10):1323-1332, 2001) as applied to claims 2 - 4, 11 - 12, 15 and 20 - 25 above, and in further view of Ochiya *et al.* (Curr. Gene Therapy 1: 31 - 52, 2001). The Office Action stated "The prior cited art does not

teach the kit or method to comprise atelocollagen. However, at the time of the invention, Ochiya *et al.* reviewed the advantages of using atelocollagen to mediate controlled-release of bioactive agents of molecular medicines."

Additionally, the Office Action stated that the applicant did not, in response to the previous Office Action, argue the difficulties of combining the atelocollagen of Ochiya *et al.* with the virus of Terman '551 and the cells of Harrison *et al.* The Examiner also stated that the components of the present invention are disclosed in the references, and that a person skilled in the art can easily conceive the present invention.

The Applicants disagree with the conclusion of the Office Action that the combination of Terman '551, Harrison *et al.*, and Ochiya *et al.* discloses, each and every feature, of Claims 6 and 16, and Traverse.

As discussed above, Terman '551 does not disclose, each and every feature, of Independent Claims 24 and 25, and neither Harrison *et al.* nor Ochiya *et al.*, individually or in combination with Terman '551 disclose those features which are deficient in Terman '551. Therefore, the disclosures of Harrison *et al.* and Ochiya *et al.* are not sufficient to make obvious the Claims 6 and 16, which are dependent from Claims 24 and 25.

The Examiner is requested to withdraw the combination of Terman '551, Harrison *et al.* and Ochiya *et al.* as 103(a) Prior Art references. In light of the foregoing arguments and amendments to the claims, the Examiner is respectfully requested to allow Claims 6 and 16.

35 U.S.C. § 103(a) Rejection of Claim 5

The Office Action rejected Claim 5 under 35 U.S.C. 103(a) as being obvious over Terman (2002/017755 1 Al), Harrison *et al.* (Human Gene Therapy 12(10):1323-1332, 2001), Ochiya *et al.* (Curr. Gene Therapy 1: 31-52, 2001), Alemany *et al.* (U.S. Patent 6,403,370 B1) and Barker *et al.* (Genomics 38:215-222, 1996). The Office Action stated "The prior cited art does not teach the oncolytic virus to comprise a 1A1.3B promoter. However, at the time of the invention, Alemany *et al.* disclosed a method for killing tumor target cells, the method comprising an oncolytic adenoviral vector, wherein the oncolytic adenoviral vector comprises a tumor cell-activated promoter operably linked to the adenoviral El gene. Alemany *et al.* does not disclose the use of a 1A1.3B promoter. However, at the time of the invention, Barker *et al.*

taught that the identification of the promoter region for 1A1.3B and that 1A1.3B (also known as CAl25) is an art-recognized ovarian cancer marker antigen."

The Applicants disagree with the conclusion of the Office Action that the combination of Terman '551, Harrison *et al.*, Ochiya *et al.*, Alemany *et al.* and Barker *et al.* discloses, each and every feature, of Claim 5, and Traverse.

As discussed above, Terman '551 does not disclose, each and every feature, of Independent Claims 24, and neither Harrison *et al.*, Ochiya *et al.*, Alemany *et al.*, nor Barker *et al.*, individually or in combination with Terman '551, disclose those features which are deficient in Terman '551. Therefore, the disclosures of Alemany *et al.* and Barker *et al.* are not sufficient to make obvious Claim 5, which is dependent from Claims 24.

The Examiner is requested to withdraw the combination of Terman '551, Harrison *et al.*, Ochiya *et al.*, Alemany *et al.* and Barker *et al.* as 103(a) Prior Art references. In light of the foregoing arguments and amendments to the claims, the Examiner is respectfully requested to allow Claim 5.

Double Patenting (Provisional) Rejection of Claims 2 – 6 and 20 - 24

The Office Action provisionally rejected Claims 2 - 6 and 20 - 24 under the judicially created doctrine of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1 - 5 of copending Application No. 10/575,894.

Applicants have submitted a Terminal Disclaimer with the filing of this response.

In light of the foregoing arguments and amendments to the claims, the Examiner is respectfully requested to allow Claims 2 – 6 and 20 – 24.

Amendments to Claims

No New Matter was added by the amendments to the Claims. All amendments to the claims were to correct errors in grammar, style and clarity, and not to narrow the claims to allow patentability over any cited references. The amended claims are claiming the same scope as the originally filed claims, and have not been narrowed by the amendments.

No Disclaimers or Disavowals

Although the present communication may include alterations to the claims, the Applicants are not conceding in this application that previously pending claims are not patentable. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

Claims 1 – 25 are pending. Claims 2 – 6, 11, 12, 15, 16, 20 – 23 are Currently amended. Claims 24 and 25 are New. Claims 7 – 9, 13, 14 and 17 – 19 are Withdrawn. Claims 1 and 10 are Canceled.

No fees are believed due; however, the Commissioner is authorized to charge any additional fees now and in the future which may be due, including any fees for additional extension of time, or credit overpayment to credit card information.

Date: December 22, 2008

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